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CLINICAL INVESTIGATION **Genitourinary Cancer**

LONG-TERM OUTCOMES AFTER MAXIMAL SURGICAL RESECTION AND INTRAOPERATIVE ELECTRON RADIOTHERAPY FOR LOCOREGIONALLY RECURRENT OR LOCOREGIONALLY ADVANCED PRIMARY RENAL CELL CARCINOMA

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Purpose: To report outcomes of a multimodality therapy combining maximal surgical resection and intraoperative electron radiotherapy (IOERT) for patients with locoregionally (LR) recurrent renal cell carcinoma (RCC) after radical nephrectomy or LR advanced primary RCC.

Methods and Materials: From 1989 through 2005, a total of 22 patients with LR recurrent ($n = 19$) or LR advanced primary ($n = 3$) RCC were treated with this multimodality approach. The median patient age was 63 years (range 46-78). Twenty-one patients (95%) received perioperative external beam radiotherapy (EBRT) with a median dose of 4,500 cGy (range, 4,140–5,500). Surgical resection was R0 (negative margins) in 5 patients (23%) and R1 (residual microscopic disease) in 17 patients (77%). The median IOERT dose delivered was 1,250 cGy (range, 1,000–2,000). Overall survival (OS) and disease-free survival (DFS) and relapse patterns were estimated using the Kaplan–Meier method.

Results: The median follow-up for surviving patients was 9.9 years (range, 3.6–20 years). The OS and DFS at 1, 5, and 10 years were 91%, 40%, and 35% and 64%, 31%, and 31%, respectively. Central recurrence (within the IOERT field), LR relapse (tumor bed or regional lymph nodes), and distant metastases at 5 years were 9%, 27%, and 64%, respectively. Mortality within 30 days of surgery and IOERT was 0%. Five patients (23%) experienced acute or late National Cancer Institute Common Toxicity Criteria (NCI-CTCAE) Version 4 Grade 3 to 5 toxicities.

Conclusions: In patients with LR recurrent or LR advanced primary RCC, a multimodality approach of perioperative EBRT, maximal surgical resection, and IOERT yielded encouraging results. This regimen warrants further investigation.

Intraoperative radiotherapy, Renal cell carcinoma, Nephrectomy, Combined modality therapy.

INTRODUCTION

In the United States, approximately 58,240 patients were diagnosed with cancer of the kidney or renal pelvis in 2010 (1). The majority of patients with this disease present with clinically localized renal cell carcinoma (RCC) and are candidates for potentially curative nephrectomy. However, some patients present with locoregionally advanced disease of borderline resectability. In addition, 1% to 3% of patients experience isolated locoregional (LR) recurrence in the retroperitoneal soft tissue and/or nodal basins after nephrectomy (2–5). The optimal management of isolated LR recurrent disease remains unknown, given its relative infrequency. In carefully selected patients with resectable LR recurrent disease, salvage surgery is associated with long-term survival in only a small portion of patients (2–9). In the setting of salvage or primary surgery, margin status was reported to be an important prognostic factor for survival (4, 10). However, a wide resection of tumor is often unachievable due to its close proximity or frank invasion into adjacent unresectable structures such as major vessels and/or vertebral bodies. Therefore, in patients with LR recurrence or LR advanced primary RCC of borderline resectability, it is appropriate to consider additional LR therapies adjunct to surgery to optimize LR control and survival.

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Since 1989, we have treated selected patients with isolated LR recurrence after nephrectomy or LR advanced primary RCC with a multimodality approach consisting of perioperative external beam radiotherapy (EBRT), maximal resection, and intraoperative electron radiotherapy (IOERT). In 1994, we reported favorable early outcomes in an initial cohort of patients (11). In addition, we have reported high rates of local control and acceptable toxicity with this multimodality approach for patients with other LR advanced primary or LR recurrent abdominal and pelvic tumors (12–17). Here we report long-term outcomes on an expanded series of patients with LR recurrence or LR advanced primary RCC treated with a multimodality approach incorporating IOERT.

METHODS AND MATERIALS

The prospective departmental IORT database was searched for patients with RCC treated with IOERT at Mayo Clinic, Rochester, MN. Inclusion criteria included primary or recurrent RCC treated with surgery and IOERT to LR disease as a component of potentially curative therapy. Exclusion criteria included surgery and IOERT to a distant metastatic site for palliation of symptoms only. Twenty-two consecutive patients treated between 1989 and 2005 met the above criteria and were included in this analysis. The Mayo Foundation Institutional Review Board approved this retrospective study.

Patients were selected for the multimodality approach by the surgeon and radiation oncologist because of concern that surgery alone would be unlikely to remove all gross and/or microscopic LR disease. All patients underwent pretreatment staging, typically consisting of the following: physical examination; laboratory evaluation; computed tomography (CT) of the chest, abdomen, and pelvis; bone scan; abdominal ultrasound; and/or brain imaging at the discretion of the attending physicians. In patients with recurrent disease, histologic confirmation of recurrence was obtained before treatment. Patients with resectable distant oligometastatic disease were considered candidates for the multimodality therapy.

Patients with no prior radiotherapy were treated with perioperative EBRT (either preoperatively, postoperatively, or a combination of both) to the tumor bed and regional lymphatics using megavoltage photons. Institutional preference was to deliver EBRT preoperatively (45 Gy in 25 fractions over 5 weeks to extended fields,. followed by a smaller boost field receiving 5 to 9 Gy in three to five fractions). One patient with LR recurrence had a history of prior EBRT was not given perioperative EBRT. No patients received concurrent systemic therapy.

Details regarding IOERT delivery at Mayo Clinic have been previously described and are briefly summarized here (12). After maximal surgical resection of disease, the primary surgeon and radiation oncologist determined the area of suspected microscopic residual disease. A circular (diameter, 6–9.5 cm) or elliptical (width, 6–9 cm; length, 11–15 cm) Lucite applicator encompassing the area of disease was immobilized using a Buchwalter retractor system. Retractors and lead shielding were used as needed to displace and protect critical structures adjacent to the treatment field. The applicator was then docked to the linear accelerator. Before 1989, patients were transferred from the operating room under anesthesia to the radiation oncology department for IOERT. Since 1989, IOERT has been delivered in a dedicated operating room containing a refurbished Clinic 18 linear accelerator (Varian, Palo Alto, CA). IOERT was delivered in a single fraction, with the dose selected on the basis of amount of residual disease, proximity of critical structures, and the dose of preoperative and/or anticipated postoperative EBRT.

Table 1. Patient characteristics at pretreatment evaluation

Characteristic	*n* (%)
Age, y	
Median	63
Range	43–78
Sex	
Male	17 (77)
Female	5 (23)
Disease status	
Primary	3 (14)
Recurrent	19 (86)
Grade	
2	9 (41)
3	10 (45)
4	3 (14)
Maximum locoregional tumor dimension, cm	
Median	7
Range	0–20*
Additional known site of oligometastatic disease	
No	19 (86)
Lung	2 (9)
Liver	1 (5)
Prior external beam radiotherapy	
No	21 (95)
Yes	1 (5)

* One patient with microscopic residual disease after resection at an outside institution (0 cm).

Follow-up data including survival, patterns of failure, and toxicity were recorded prospectively in an institutional IOERT database. These data were verified by retrospective chart review. Endpoints were defined from the date of surgery and IOERT. Disease progression was discerned by radiographic imaging and/or clinical examination. Central failure (CF) was defined as recurrence within the IOERT field. LR failure (LRF) was defined as failure in the tumor bed, local lymphatics, or regional lymphatics, all of which were typically included in the perioperative EBRT field. Distant failure (DF) was defined as any relapse beyond LRF. Toxicities were initially recorded using criteria developed by the National Cancer Institute (NCI) IORT working group (18). Subsequently, toxicities were reclassified using the NCI Common Toxicity Criteria Version 4 (19). The time point of 90 days after surgery and IOERT was used to distinguish between acute and late toxicity.

The Kaplan–Meier (KM) method was used to analyze survival and relapse outcomes (20). Potential factors associated with LRF and overall survival (OS) were examined in a univariate analysis using the log-rank test. Variables examined included gender (male vs. female), age (< median vs. ≥ median), histologic grade (2 vs. 3 or 4), time to recurrence after nephrectomy (< median vs. ≥ median), advanced primary vs. recurrence, size (< 5 cm vs. ≥ 5 cm), resected oligometastatic disease (yes vs. no), margin status (negative [R0] vs. microscopic positive [R1]), and IOERT dose (< median vs. ≥ median). A p value < 0.05 was considered significant. Follow-up data were collected through March 2010. Statistical analysis was performed with JMP 8.0 (SAS Institute Inc., Cary, NC)

RESULTS

Patient characteristics are detailed in Table 1. Three patients had LR advanced primary disease with extensive